REMARKS

FORMAL MATTERS

Claims 1-5, 8, 10, 13-20, 22, 27-28, 30-35 and 40 are pending after entry of the amendments set forth herein.

Claims 6-7, 9, 11-12, 21, 23-26, 29, 36-39 and 41 are canceled.

Claims 1-5, 8, 10, 13-15, 28 and 32-35 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments can be found throughout the specification, and at, for example, page 6, lines 1-6. Accordingly, no new matter is added by these amendments.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

REQUEST FOR EXAMINER INTERVIEW

Applicants hereby request an interview with the Examiner in order to further address any rejection or objection that may be outstanding following the submission of this communication. The Examiner is requested to contact the undersigned at his earliest convenience.

OBJECTION TO TITLE

The Office Action states that the "title of the invention will have to be changed to more closely reflect the claims".

The title has been amended to reflect that methods are claimed in addition to the transgenic non-human mammal.

REJECTION UNDER §101 AND §112, ¶1 – UTILITY AND ENABLEMENT

Claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 were rejected under §101 on the grounds the claimed invention lacks patentable utility. The Examiner issued a parallel rejection under §112, ¶1 on the same grounds on the reasoning that since the claimed invention is not supported by a specific, substantial asserted, or well-established, utility, then the specification fails to satisfy the how-to-use prong of §112, ¶1. These rejections are respectfully traversed as applied and as it may be applied to the

amended claims.

Each aspect of the rejection is addressed below in turn.

C5aR

The Examiner asserts that the specification and the art at the time of filing do not disclose any diseases effected by C5a binding to C5aR or by C5aR mutations in humans. In support of this rejection, the Examiner refers to a publication by Monk (2007),[1] which the Examiner asserts stands for the proposition that the function of C5aR was previously misunderstood. Applicants respectfully disagree with the Examiner's analysis of Monk (2007).

First, Applicants note that, as stated in the abstract, Monk (2007) is a review that "highlights major developments in C5a receptor research that support C5aR as an important therapeutic target." This statement alone suggests that Monk (2007) appreciates that human C5aR is involved in human disease. In addition, Monk (2007) states in the abstract:

> Our understanding of physiology of C5a receptors ***has improved*** significantly in recent years ***through exploitation of receptor knockout and knockin mic***e, C5 and C5a antibodies, soluble recombinant C5a and C5a analogues and newly developed receptor antagonists.

(emphasis added)

This statement in Monk (2007) does not stand for the proposition that the role of human C5aR was previously misunderstood. Instead it indicates that the understanding of the role of human C5aR by 2007 came to be understood *even better* through use of these knock-out and knock-in mice.

The use of a portion of the sentence from the abstract of the Monk (2007) review article to suggest that there is nothing in the specification (or art) at the time of filing disclosing a role for C5a in human disease is misleading. Monk (2007) is a review article covering many years of research relating to C5a and C5a receptors. Statements made in such a review must be read in the context of the reference. Use of the word 'recent' in a review article that covers about 30 years of work in the field should not be taken to mean so recent as to mean at the time of the priority application filing of the instant application, i.e., 2003.

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[1] Monk (2007) British J. Pharm. 152:429-448.

Monk (2007) at page 431 provides a list of the human diseases and experimental models of disease in which C5a has been implicated, the majority of which were published before the instant application's priority date of December 24, 2003. Table 2 of Monk (2007) also points out that numerous publications describe work with a C5aR antagonist (3D53 and its analogues) to demonstrate that it is the interaction between C5a and one of its receptors, C5aR, that is responsible for the deleterious role of C5a in models of human diseases (Monk (2007), page 437). Many of the publications in Table 2 were published prior to 2003. Thus Monk (2007) provides evidence that around December 2003, the time of the priority application, the ordinarily skilled artisan in the relevant field had clear appreciation of the important role of C5aR in human disease. In addition, the instant application does, in fact, disclose specific examples of the role of C5aR in human disease, see, e.g., specification page 38, line 11 to page 44, line 12.

Using the mice as models for disease

The Examiner has asserted that there is nothing in the specification to show that the human C5aR knockin correlates to a naturally occurring mutation found in humans or that the transgenic mice have a phenotype that models a disease. Applicants respectfully submit the Examiner's conclusion is in error.

The specification as filed indicates that, at the time of the invention, it was understood that signaling of C5aR is involved in a range of diseases and that agonists/antagonists of C5aR have therapeutic applications (see, for example, the Background section on pages 1-3).

Furthermore, the diseases are not induced in the claimed transgenic mice by the introduction of the humanized C5aR sequence. Instead, disease is induced in the claimed transgenic mice following administration of an exogenous substance. This is exemplified in the specification by the use of K/BxN serum, which induces a state in the claimed transgenic mice that serves as a model of human arthritic disease.

The presence of the humanized C5aR makes the mouse model much more useful in screening for drugs that will be effective in humans. Because a human or humanized C5aR is present in the mice, the model more closely models human disease. The human or humanized C5aR functions in the mouse in a manner similar to that of the mouse receptor, with the additional function that it will facilitate a response to drugs that more closely models that found in the human immune system. Drugs that have been developed to date target the human C5a receptor and thus work more efficiently in humans than in rodents. In conventional rodent disease models, much higher concentrations of a drug must be used to

observe an effect of compound being screened, with the result that toxicity or off-target effects in rodents can complicate interpretation of the data.

Using the mice to identify compounds that modulate C5aR

At page 4 of the Office Action the Examiner states:

> It is unclear how the "homozygous hC5aR and wild-type (control) mice" are "in the K/BxN model" as described by applicants; the specification does not clearly set forth that knockin mice and wild-type mice were both given K/BxN sera.

The specification at page 60, lines 11-15 describes injection of K/BxN sera into homozygous C5aR and wild-type control mice. The phrase "in the K/BxN model" as used on page 62 of the specification is a discussion of the results obtained in Example 6, and therefore describes the results of injecting homozygous C5aR and wild-type control mice with K/BxN sera as described on page 60 of the specification.

The Examiner also seems to have misunderstood the results presented in Figure 7 as well as the discussion relating to testing of the claimed mouse models with a known anti-C5aR antibody designated 7F3 (see specification page 61, lines 29 to 35. The Examiner asserts that it was already known that the anti-human C5aR antibody (7F3) targeted hC5aR and not mouse, so the controls required to identify compounds that specifically target hC5aR using the mice claimed are not described by the applicants. Applicants respectfully submit that a person of ordinary skill in the art would understand that a potential novel compound that antagonizes C5aR could be tested by simply administering that compound to the knockin mice of the K/BxN model and using as a control, for example, an antibody of the same isotope but irrelevant specificity. This is suggested in the specification at page 62, lines 23-24.

Indeed, *because* the anti-C5aR antibody 7F3 was already known to bind to human C5aR, it was used to verify that the claimed mouse model is suitable for screening antagonists of C5aR. It would be clearly understood by the ordinarily skilled artisan that, in light of these results, the mouse model could be used to screen for new compounds that target C5aR. The Examiner's statement that the alleged use is merely using the knockin to screen anti-inflammatory compounds already known to target human C5aR fails to take into account that the specification is, in fact, providing a proof of principle.

Conclusion

In view of the arguments above, Applicants submit that the rejection of the claims under §101 should be withdrawn.

REJECTION UNDER §112, ¶1 – ENABLEMENT (SCOPE)

Claims 1-5, 8, 10, 12, 14-20, 22, 27, 28, 30-35 and 40 were rejected under §112, ¶1 on the grounds that the claims are not supported by an enabling disclosure to their full scope. The Examiner stated that "the specification does not teach how to make any other rodents . . . or the cDNA of other rodents other than mice." This rejection is respectfully traversed as applied and as it may be applied to the presently pending claims.

The claims are presently amended to recite "transgenic mouse or rat".

The specification provides evidence that mouse C5a is capable of binding to and effecting signaling of human or humanized C5aR. As shown in the alignment of Exhibit 1 (attached), mouse and rat C5a share over 80% sequence identity. In view of this, the ordinarily skilled artisan would reasonably expect that, like mouse C5a, rat C5a would also bind to and effect signaling of human or humanized C5aR. Furthermore, the ordinarily skilled artisan could readily produce a knockin transgenic rat based on the information provided in the specification.

REJECTIONS UNDER §103(A)

The Examiner has maintained the rejection of claims 1-5, 8, 10, 13-20, 22, 27, 28, 30-35 and 40 as allegedly being obvious over Sato (Thrombosis and Haemostasis (1999) 82(2):865-869- henceforth "Sato"), Roebroek (Methods in Molecular Biology (2003) 209:187-200- henceforth "Roebroek"), Homanics (Methods in Alcohol Related Neuroscience Research (2002), pg 31-61- henceforth "Homanics"), Lester et al, (Curr. Opin. Drug Discov. and Dev. (2003) 6(5):663-639-henceforth "Lester"), Champtiaux (Curr. Drug Targets, CNS & Neuro. Dis.(2002)1:319-330- henceforth "Champtiaux"), Girardi et al., (J.Clin. Invest. (2003) 112(11):1644-1654- henceforth "Girardi") in view of Burmer et al., (WO 02/61087- henceforth "Burmer").

The Examiner maintains that the claims are obvious in light of the cited prior art providing knockin techniques and the sequence of C5aR. In particular, the Examiner maintains that a person skilled in the art would have been motivated to knockin the human C5aR gene to test functional redundancy and, that without evidence to the contrary, the results obtained would have been expected.

The Examiner further asserts that, since the claims do not require that the human C5aR binds mouse C5a or causes chemotaxis of leucocytes, all that is required by the claims are mice expressing the human C5aR gene.

This rejection is respectfully traversed as applied and as it may be applied to the claims as now pending.

The Court in *KSR* repeatedly emphasized that an obviousness inquiry must take into account the predictability of the field:[2]

> one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

(emphasis added)

The references upon which the Examiner relies for this rejection are merely a collection of papers describing techniques for generating knock-in or knock out mice, along with a paper providing the human C5aR sequence. At the time of the claimed invention, the ordinarily skilled artisan would not expect that human C5aR signaling would be activated by mouse C5a, or that it would function in an in vivo mouse model.

C5aR is a G protein coupled receptor (GPCR). The ligand for C5aR, C5a, is a large peptide. G protein coupled receptors with large peptide ligands typically have as little as 70% amino acid identity between species. Most of the diversity in these GPCRs lies in the cell surface loops – the region(s) of ligand binding. Mouse and human C5a ligand, as well as the mouse and human C5aR, share only about 70 % amino acid sequence identity. This is illustrated in the amino acid sequence alignments of mouse and human C5a (Exhibit 2) and the mouse and human extracellular domains of the C5aR (Exhibit 3). This sequence diversity between human and mouse C5a, and between human and mouse C5aR, was known at the time of the priority application (December 2003). For at least this reason, the ordinarily

skilled person would not have predicted at that time that mouse C5a would bind human C5aR.

This argument is further supported by the report by Woodruff et al. in 2001 (Woodruff et al., (2001) Inflammation, 25:171-177, Exhibit 4). Woodruff et al. points out the cross-species difficulties in using small peptide agonists and antagonists. This provides further evidence that it was unpredictable that mouse C5a would activate the human receptor when expressed in vivo in knock-in mice.

Indeed, the cross species functions of anaphylatoxin ligands, such as C5a, were well known to be unpredictable around December 2003. For example, human C4a was also well known as an anaphylatoxin. Human C4a was able to cause contractions of guinea pig ileum, and cross-desensitized in this assay with C3a (Hugli et al. (1983) Mol Immunol, 20:637-645, Exhibit 5). However, when the human C3a receptor was cloned, it was demonstrated that human C4a interacted uniquely as an agonist with the guinea pig C3a receptor, *but did not interact at all with the human C3a receptor* (Lienenklaus et al. (1998) J Immunol, 161:2089-2093, Exhibit 6).

Thus, in view of this state of the art at the relevant time of December 2003, the filing date of the priority application of the instant application, it was *not predictable* that a mouse or rat C5a would bind a human or humanized C5aR. Indeed, the state of the art would lead one to conclude that the mouse C5aR would be unlikely to bind to and effect signaling of human C5aR. Thus, the Examiner's assertion that the results achieved by the claimed invention are "expected" is unfounded in view of the state of the art at the relevant time.

For at least these reasons, Applicants submit that the rejection of the claims under §103(a) should be withdrawn, which action is respectfully requested.

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[2] *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, slip p. at 13 (U.S. 2007). ***[NOTE: Cite to be corrected prior to filing.]***

CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number RICE-050.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: November 16, 2009

By: /Carol L. Francis, Reg.No.36513/
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Enclosure(s):

Exhibit 1:	Alignment of Amino Acid Sequences of Mouse And Rat C5a
Exhibit 2:	Alignment of Amino Acid Sequences of Mouse And Human C5a
Exhibit 3:	Alignment of Amino Acid Sequence of Human Mouse and Rat C5aR Extracellular Domains Involved In Ligand Binding
Exhibit 4:	Woodruff et al., (2001) Inflammation, 25:171-177
Exhibit 5:	Hugli et al. (1983) Mol Immunol, 20:637-645
Exhibit 6:	Lienenklaus et al. (1998) J Immunol, 161:2089-2093
Exhibit 7:	Lee et al. (2006) Nat Biotechnol, 24:1279-1284

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